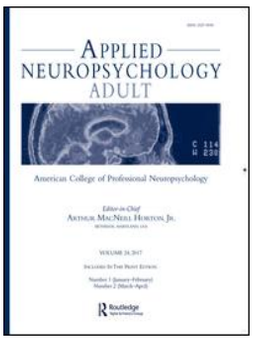

Applied Neuropsychology: Adult

ISSN: 2327-9095 (Print) 2327-9109 (Online) Journal homepage: https://www.tandfonline.com/loi/hapn21

Maintenance of multi-domain neurocognitive functions in patients with newly-diagnosed primary CNS lymphoma after primary cranial radiotherapy combined with methotrexate-based chemotherapy: A preliminary case-series study

Shinn-Yn Lin, Chi-Cheng Chuang, Din-Li Tsan, Yu-Shin Hung, Chen-Ju Fu, Yi-Liang Shen, Yin-Yin Chiang, Yin-Cheng Huang, Yu-Jen Lu & Chi-Cheng Yang

To cite this article: Shinn-Yn Lin, Chi-Cheng Chuang, Din-Li Tsan, Yu-Shin Hung, Chen-Ju Fu, Yi-Liang Shen, Yin-Yin Chiang, Yin-Cheng Huang, Yu-Jen Lu & Chi-Cheng Yang (2020): Maintenance of multi-domain neurocognitive functions in patients with newly-diagnosed primary CNS lymphoma after primary cranial radiotherapy combined with methotrexate-based chemotherapy: A preliminary case-series study, Applied Neuropsychology: Adult, DOI: 10.1080/23279095.2020.1749630

To link to this article: https://doi.org/10.1080/23279095.2020.1749630

APPLIED NEUROPSYCHOLOGY: ADULT
https://doi.org/10.1080/23279095.2020.1749630

Maintenance of multi-domain neurocognitive functions in patients with newly-diagnosed primary CNS lymphoma after primary cranial radiotherapy combined with methotrexate-based chemotherapy: A preliminary case-series study

Shinn-Yn Lin[a,b]*, Chi-Cheng Chuang[c,d]*, Din-Li Tsan[d,e]*, Yu-Shin Hung[f], Chen-Ju Fu[g], Yi-Liang Shen[a], Yin-Yin Chiang[a], Yin-Cheng Huang[c,d], Yu-Jen Lu[c,d], and Chi-Cheng Yang[h,i]

[a]Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [b]Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [c]Department of Neurosurgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [d]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [e]Department of Radiation Oncology, Chang Gung Memorial Hospital, Keelung, Taiwan; [f]Department of Hematology and Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [g]Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [h]Department of Psychology, National Chengchi University, Taipei, Taiwan; [i]Holistic Mental Health Center, Taipei City Hospital, Taipei, Taiwan

ABSTRACT

Conventional treatment for treating primary central nervous system lymphoma (PCNSL) has consisted of either whole-brain radiotherapy (WBRT) or methotrexate (MTX)-based combined modality therapy. However, delayed cognitive sequelae have emerged as a significant debilitating complication in PCNSL patients. A prospective observational case-series study with prospective assessments of neurocognitive functions (NCFs), neuroimaging, and activities of daily living in newly-diagnosed PCNSL patients was undertaken. A battery of neuropsychological measures, used to evaluate NCFs, is composed of ten standardized NCF tests, representing four domains sensitive to disease and treatment effects (executive function, attention, verbal memory, psychomotor speed), and activities of daily living. A total of 15 patients with newly-diagnosed PCNSL were consecutively enrolled in this study. Comparing the NCF scores between the baseline (before WBRT) and post-treatment (after combined chemoradiation therapy) intervals (Mean = 122.33 days, SD = 34.49, range = 77–196), neurobehavioral outcomes consistently remained improving or stable in almost each domain of NCF. Specifically, the scores on Paced Auditory Serial Addition Test—Revised (PASAT-R) were significantly improved between the baseline and post-chemoradiation assessment. Under the multidisciplinary treatment guidelines for treating patients with newly-diagnosed PCNSL, multi-domain NCF become stabilized and even improved after the course of conformal WBRT combined with or without MTX-based chemotherapy.

KEYWORDS

Neurocognitive functions (NCFs); primary central nervous system lymphoma (PCNSL); whole-brain radiation therapy (WBRT)

Introduction

Primary central nervous system lymphoma (PCNSL) is uncommon in immunocompetent individuals without acquired immune deficiency syndrome (AIDS; Fine, 1993). PCNSL accounts for <5% of all primary central nervous system (CNS) neoplasms. It is an aggressive form of non-Hodgkin lymphoma (NHL) that develops in the brain, leptomeninges, spinal cord, or eye with no evidence of other extracranial involvement. Nonimmunosuppressed patients have a more favorable prognosis than those with AIDS (Norden et al., 2011). Survival outcomes of patients with newly diagnosed PCNSL have improved over the years with treatment advances (Fine, 1993; Norden et al., 2011).

Before the 1990s, whole-brain radiation therapy (WBRT) and steroids were the first-line treatment options for generally managing patients with PCNSL. Although WBRT might contribute to high remission rates initially, the relapse rate was high, resulting in a 5-year overall survival of <20% (Kasenda et al., 2016; Reni et al., 1997). To improve the dismal outcomes in patients with PCNSL treated with WBRT alone, chemotherapy has been added to WBRT (Deangelis et al., 1992; DeAngelis et al., 2002). Methotrexate (MTX) is the most effective agent against PCNSL. Such combined modality therapy has improved therapeutic outcomes, but intracranial lymphoma relapse continues to be a major challenge. Moreover, WBRT-related delayed neurological toxicity might be a serious complication (Correa et al., 2007; Doolittle et al., 2013). To overcome the aforementioned clinical dilemmas, high-dose MTX (3.5 g/m^2 or higher) was used for treating patients with PCNSL, which resulted in improved survival outcomes (Ferreri et al., 2009; Schaff &

CONTACT Chi-Cheng Yang yangyang@nccu.edu.tw Department of Psychology, National Chengchi University, No. 64, Sec. 2, ZhiNan Rd, Taipei 11605, Taiwan; Chi-Cheng Chuang ccc2915@cgmh.org.tw Department of Neurosurgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan 333, Taiwan; College of Medicine, Chang Gung University, No. 5, Fu-Shin Street, Guishan Dist, Taoyuan 33302, Taiwan.
*These three authors have contributed equally to this manuscript as first authors.

Grommes, 2018). Accordingly, WBRT would be de-escalated or even deferred if complete remission can be achieved with upfront high-dose MTX-based regimen (Morris et al., 2013).

In terms of managing patients with primary brain malignancies including PCNSL, we are usually familiar with common therapeutic and neuro-oncological outcomes, such as intracranial disease control, progression-free survival, and overall survival (Norden et al., 2011). Moreover, assessment of neurobehavioral outcomes in patients with newly diagnosed PCNSL has been emphasized (Correa et al., 2007, 2009, 2012). For example, Correa and colleagues (2012) compared cognitive functions between 24 patients with PCNSL who received WBRT combined with chemotherapy and 26 patients with PCNSL who received chemotherapy alone. The results showed significantly more impairment of attention, verbal memory, and quality of life in patients with WBRT and chemotherapy than in those with chemotherapy only. As the changes in cognitive functions after treatment for patients with PCNSL were still unclear, the present case-series study used a standardized neurobehavioral test battery to prospectively assess multidomain cognitive functions and changes in patients with newly diagnosed PCNSL who were treated with a course of combined chemoradiation. Specifically, it is hypothesized that performances of patients' NCFs will not significantly change between baseline and post-treatment evaluation.

Methods

Participants

A total of 15 patients with newly diagnosed PCNSL were prospectively and consecutively enrolled between February 2014 and January 2018. All the participants provided written informed consent, and the study protocol was approved by the institutional review board (IRB) of our institute (IRB 102-5392B).

All patients had a histopathological diagnosis of NHL documented in their brain biopsy report. Those who had an inconclusive biopsy or who were not candidates for biopsy might be eligible for this study if they underwent typical cranial or intracranial magnetic resonance imaging or computed tomography (CT) and met at least one of the following two criteria: (1) a positive cerebrospinal fluid cytology for lymphoma cells or monoclonal lymphocyte proliferation as defined by cell surface markers; and (2) a biopsy of the vitreous or uvea demonstrating the presence of NHL cells. To exclude the possibility of secondary CNS involvement in systemic lymphoma and ensure that patients had truly newly diagnosed primary CNS lymphoma, patients were confirmed to have a normal or negative pretreatment systemic evaluation including a bone marrow aspirate and biopsy; a CT scan of the chest, abdomen, and pelvis; and an adequate bone marrow reserve.

The exclusion criteria for this study were a history of major psychiatric disease, prior cranial irradiation, preexisting immunodeficiency status such as a renal or hepatic transplant recipient, and other active primary cancer with the exception of skin basal cell carcinoma and cervical carcinoma in situ.

Neurocognitive assessments

A standardized test battery (Table 1) was used to evaluate different domains of neuropsychological functions, which mainly included verbal memory, executive functions, and information processing. Four subtests from the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; Wechsler, 1997), namely Similarities, Arithmetic, Block Design, and Digit Symbol Coding, were selected to capture the patients' multidomain intelligent functioning. The age-corrected scaled scores of each subtest were recorded.

Subsequently, to assess verbal memory, the Taiwan Word Sequence Learning Test (TWSLT; Hua, 1986) was administered to measure the auditory verbal learning ability. The TWSLT examines immediate recall with a 10-trial presentation of six Chinese semantically meaningless words (scores from 0 to 60). After a 10-min delay, three retention processes were evaluated: the free recall (scores from 0 to 6), cued recall (scores from 0 to 6), and recognition of the target words presented with distracters (scores from 0 to 30).

Executive functions were examined through the Modified Card Sorting Test (MCST; Nelson, 1976), Trail Making Test (TMT; Reitan, 1958), and Semantic Association of Verbal Fluency Test (SAVF; Hua et al., 1997). The MCST is a card sorting test with 48 cards. Each card involves three semantic categories: shape, color, and number. Participants are required to sort cards based on their intuitive styles of mental categorization. The performances of completed category (CC) and perseverative errors (PE) were recorded to present the functions of conceptual formation and mental shifting.

The TMT is an easily administered test of visuomotor sequencing and cognitive flexibility. The reaction time spent on each worksheet is recorded as the score of the TMT. Lastly, the SAVF consists of three semantic categories: fruits, fishes, and vegetables. Participants are asked to report as many items belonging to a given category as possible within 1 min. The score was a summation of correct responses the assessed participant could achieve within the three categories.

Moreover, information processing was evaluated using the Paced Auditory Serial Addition Test–Revised (PASAT-R; Levin, 1983). The PASAT-R contains 26 randomized digits in each trial, with 100 possible responses from all four trials. Participants were required to add pairs of digits in a sequence of digits, so that each digit was added to the one immediately preceding it, and the presentations of digits were at four rates of speed, differing by 0.4 s and ranging from 1 to every 1.6–2.8 s. The summation of correct responses in four trials was recorded.

Combined chemoradiation for treating newly diagnosed PCNSL patients

According to treatment protocols and guidelines for managing patients with PCNSL, each patient with newly diagnosed PCNSL should be treated with combined chemoradiation in a sandwiched manner, during which two cycles of induction chemotherapy with intravenous MTX (MTX at a

Table 1. A selective neurocognitive test battery employed in this prospective observational study.

Neurocognitive tests	Domain	Description
WAIS-III: Wechsler Adult Intelligence Scale – 3rd version (WAIS-III)		
Similarities	Verbal comprehension	To measure the ability of abstract verbal reasoning and semantic knowledge
Arithmetic	Working memory	Related to prefrontal cortex
Block design	Perceptual organization	Related to parietal and frontal cortex A measure of spatial visualization ability and motor skill
Digit Symbol Coding (DS)	Psychomotor speed	Related to white matter tract A measure of the speed of visual-perceptual discrimination and scanning
Verbal capability		
Word Sequence Learning Test (WSLT)	Verbal memory Immediate recall Delayed recall	To evaluate auditory memory of verbal information without context
Executive functions		
Modified Card Sorting Test (MCST)	Executive function	Related to conceptual formation and mental shifting
Trail Making Test (TMT)	Speed and flexibility	Related to speed and flexibility A measure the ability of visual attention and task switching
Semantic Association of Verbal Fluency (SAVF)	Verbal fluency	Related to frontal and temporal cortex A measure of the ability of phonemic and semantic variants
Information processing		
Paced Auditory Serial Addition Test—Revised (PASAT-R)	Information processing	To assess the capacity and speed of information processing, as well as sustained and divided attention

conventional dose of 1 g/m^2) and intrathecal MTX (12 mg, given twice weekly for totally six doses) are followed by a complete course of intracranial radiotherapy and then finally high-dose cytarabine for two cycles.

Radiation therapy: treatment planning and delivery

Regarding the prescription of the RT volume and dose, the WBRT course was administered between the initial cycles of MTX usually at a conventional dose of 1 g/m^2 and the subsequent cycles of systemic chemotherapy with Ara-C. The clinical target volume of the whole brain was generally irradiated with a highly conformal treatment plan using volumetric modulated arc therapy rather than laterally opposed fields with 30–39.6 Gy, followed by an additional and approximate 10 Gy involved-site boost, particularly in patients with intracranial lymphoma displaying partial response to the initial conventional MTX doses. Furthermore, this 10 Gy involved-site focal boost could be delivered using the technique of simultaneously integrated boost (SIB) incorporated into the course of conformal WBRT.

Procedure

Patients undergoing combination chemoradiation were evaluated and followed up at predetermined time points. The crucial time point of NCF follow up was scheduled shortly after completing the entire course of combined and sandwiched chemoradiation (Mean = 122.33 days, SD = 34.49, range = 77–196).

Data analysis

The exact significance of the paired differences in various NCF scores (means or mediums) between two time points was quantitatively analyzed using the Wilcoxon signed-rank test due to the small sample size of the present study. It was considered statistically significant when $p < 0.05$. The software of Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, IL) was used for data analysis.

Results

As shown in Table 2, the median age of the first PCNSL diagnosis was 56 years, ranging from 36 to 77 years. Regarding performance status at the first PCNSL diagnosis, the majority of our studied patients had a fair or good performance status denoted by Eastern Cooperative Oncology Group (ECOG) 1 or 0, respectively, whereas the remaining one-third of patients ($n = 5$) had a barely satisfactory performance status represented by ECOG 2. Regarding the involved sites of intracranial lymphoma, the majority of patients had multifocal and deep-seated lesions such as basal ganglia, thalamus, caudate nucleus, and corpus callosum. With regards to the prescribed dose for irradiating the whole brain, the median cumulative dose and fractionation were 3,960 cGy in 22 fractions in 1.8-Gy fractions. Additionally, the prescribed dose tailored to the involved site or tumor bed generally ranged from 4,320 to 5,360 cGy, except for the two patients diagnosed as having primary intraocular lymphoma and one patient experiencing lethal septic shock resulting from the upfront MTX-based chemotherapy.

Regarding neurocognitive outcomes, excluding one male patient who was reluctant to be evaluated due to personal

Table 2. Demographical information of consecutively enrolled patients.

Patients	Sex	Age	ECOG performance status	Involved site(s)	WBRT dose (cGy)	ISRT dose (cGy)	Interval$^{\Theta}$ (days)	Interval$^{\beta}$ (days)	Interval$^{\Delta}$ (days)
A001	F	36	1	Right frontal	3,600	4,800	−2	116	118
A002	F	51	1	Left temporal	3,960	5,360	−2	87	91
A003	M	56	2	Bilateral corpus callosum, left cerebral peduncle	3,960	5,040	−2	95	99
A004	M	77	2	Left thalamus, left basal ganglion	2,880	2,800	−4	NA	NA
A005	M	56	2	Right corona radiata, right thalamus	3,060	5,040	−2	88	92
A006	F	62	1	Right parietal	3,600	4,320	−2	115	128
A007	M	70	1	Vitreous body	4,000	3,000	−1	193	196
A008	F	40	1	Right anterior basal frontal, Periventricular, right striatum & thalamus, right temporal horn, right septum pellucidum	3,960	4,752	−1	171	176
A009	F	57	0–1	Periventricular, bilateral caudate nuclei, corpus callosum	3,960	5,040	−2	129	133
A010	F	50	1	Left thalamus, midbrain	3,960	5,160	−33	NA	NA
A011	M	39	0–1	Vitreous body	4,060	3,060	−5	121	126
A012	F	54	2	Periventricular white matter lesions, left peritrigonal	3,960	4,752	−3	116	119
A013	F	58	1	Right basal ganglion, internal capsule, right cerebral peduncle	3,600	5,320	−6	69	77
A014	M	59	1	Left basal ganglion	3,960	5,040	NA	NA	NA
A015	F	67	2	Left frontal, left striatothalamic, left cerebral peduncle	3,960	4,752	−6	107	113

M: Male; F: Female; RT: Radiation therapy; WBRT: Whole-brain radiation therapy; ISRT: Involved-site radiotherapy. Various time intervals (in days) between the start of the course of WBRT and the administration of NCF testing are disclosed to demonstrate the time span and sequence in relation to the start date of baseline NCF assessment. Accordingly, a negative value indicates the time point of performing NCF assessment is before initiating the course of brain irradiation; a positive value signifies that NCF testing is administered after the course of brain irradiation has been initiated. Interval$^{\Theta}$ represents the number of days between pre-RT NCF assessment and the start of the WBRT course; Interval$^{\beta}$ basically means the number of days elapsing from the start of the course of brain irradiation to the completion of all scheduled combined chemoradiation. At last, Interval$^{\Delta}$ signifies the time interval in days from the pre-RT NCF assessment to the assessment after completion of all scheduled combined chemoradiation.

reasons even after he had signed the informed consent. The original data on neurocognitive performance in our 15 studied patients are presented in Table 3. As illustrated in Figure 1, the baseline NCF assessment was consistently performed just before initiating the course of WBRT, which was delivered after patients received upfront chemotherapy with MTX. Figure 1a shows the baseline values of some subsets of the WAIS-III; most patients failed to attain the lower limit of the normal range of the general population (For a scaled score of WAIS-III Subtests, Mean = 10, SD = 3). By contrast, the neurocognitive status consistently stabilized and even improved to some extent after the entire course of combined chemoradiation. Similarly, as presented in Figure 1b, a trend was observed toward neuropsychological stabilization and even improvement in patients' verbal memory represented by the TWSLT, both in immediate recall and recognition of verbal memory.

Furthermore, our results (Figure 1c) clearly showed that both information processing determined using PASAT-R and executive function determined using SAVF showed a tendency toward neurocognitive stabilization and improvement.

As shown in Table 4, the cognitive improvement in information processing evaluated using PASAT-R was significant between immediate posttreatment and baseline assessments ($Z = -2.40$, $p = 0.02$). In addition, patients' executive function (Figure 1d and Table 4) regarding mental shifting represented by the performance in the TMT exhibited an improving tendency, particularly for the part B of the TMT, with borderline statistical significance ($Z = -1.89$, $p = 0.06$). As shown in Figure 1e and Table 4, the completed categories of the MCST presented with a stabilizing and improving trend ($Z = -2.25$, $p = 0.02$).

Discussion

In this era of remarkable advances for radiotherapeutic planning and delivery of WBRT, almost all neurocognitive testing in the current study exhibited a consistent tendency toward cognitive stabilization without any evidence of NCF decline after patients had undergone the entire course of scheduled combined chemoradiation.

For approximately two decades, for treating patients with newly diagnosed PCNSL, combined chemoradiation was administered in a sandwiched manner, in which the WBRT course is delivered and sandwiched between the upfront courses of intravenous and intrathecal MTX and two final courses of chemotherapy with Ara-C. On the basis of the notion that whole-brain irradiation might be the most critical factor influencing patients' neurocognitive performance after cytotoxic treatment, the time point of administering "baseline" NCF assessment was reasonably presumed to be just before initiating the course of WBRT after receiving initial MTX courses. It is thus strongly emphasized that selecting and deciding the timing of administering neurobehavioral assessments should be considered, and the "baseline" NCF assessment in the current study was administered just before initiating the WBRT course.

Table 3. Scores of the Wechsler Adult Intelligence Scale – 3rd version, verbal memory, information processing, and executive functions.

	WAIS-III								Verbal memory				Information processing	
	Similarities		Arithmetic		Block Design		DSS		WSLT-C		WSLT-R		PASAT-R	
Patients	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
A001	6	4	1	6	3	3	5	6	42	48	27	30	40	67
A002	2	1	1	1	1	3	3	3	31	39	24	23	11	26
A003	6	3	2	5	3	6			33	29	30	15	28	10
A004	5		5		5		5		50		17		4	
A005	7	8	3	4	5	6	8	10	41	41	26	26	35	64
A006	9	9	7	6	6	7	7	9	37	28	22	25	17	42
A007	3	5	7	7	11	12	9	11	18	31	19	20	41	48
A008	9	11	10	9	9	7	8	5	56	55	27	29	66	60
A009	6	7	5	6	6	9	8	9	32	46	18	27	34	46
A010	5		5		2		1		37		12		21	
A011	9	9	13	13	12	13	4	4	39	55	30	30	64	86
A012	6	9	4	11	3	3	2	7	41	54	26	29	1	53
A013	11	10	7	9	4	8	13	16	26	52	28	30	34	80
A014														
A015	3	2	2	2	1	3			13	11	18	19	0	0

	Executive functions									
	SAVF		MCST-CC		MCST-PE[a]		TMT(A)[b]		TMT(B)[b]	
Patients	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
A001	35	36	1	4	3	7	44.6	30.4	207.8	123.0
A002	36	22	1	2	9	15	105.5	95.2	230.4	214.9
A003	17	16	0	1	46	14	80.2	85.3	164.8	190.3
A004	12		1		11		101.8			
A005	32	35	3	6	20	5	65.11	53.2	139.1	129.5
A006	19	29	4	3	2	15	111.5	55.9	259.0	
A007	49	38	3		4		64.8	49.6	204.1	209.7
A008	36	34	6	6	7	1	39.7	44.6	100.3	83.9
A009	37	42	0	2	21	4	53.7	35.3	184.1	148.4
A010	13		1		0		205.8			
A011	34	37	7	7	11	0	52.4	50.9	94.0	74.9
A012	26	49	3	7	11	0	181.9	53.1	353.2	106.4
A013	25	49	2	7		1	35.3	25.7	94.9	89.7
A014										
A015	4	4	1	1	13	24	468.1	542.3		

Pre: Pretreatment neurocognitive evaluation; Post: Post-treatment neurocognitive evaluation; DSS: Digit Symbol Substitution; WSLT-C: Word Sequence Learning Test – Correct; WSLT-R: Word Sequence Learning Test – Recognition; PASAT-R: Paced Auditory Serial Addition Test – Revised; SAVF: Semantic Association of Verbal Fluency; MCST-CC: Modified Card Sorting Test – Complete Categories; MCST-PE: Modified Card Sorting Test – Perseverative Errors; TMT (A): Trail Making Test part A (seconds); TMT (B): Trail Making Test part B (s).

[a]A higher score of MCST-PE indicates a less favorable performance.

[b]The unit of these numbers is "seconds." The performance of TMT indicates the speed at which the assessed patient takes this NCF examination. Therefore, the less the time in seconds is taken to complete this assessment, the better performance this assessed NCF is.

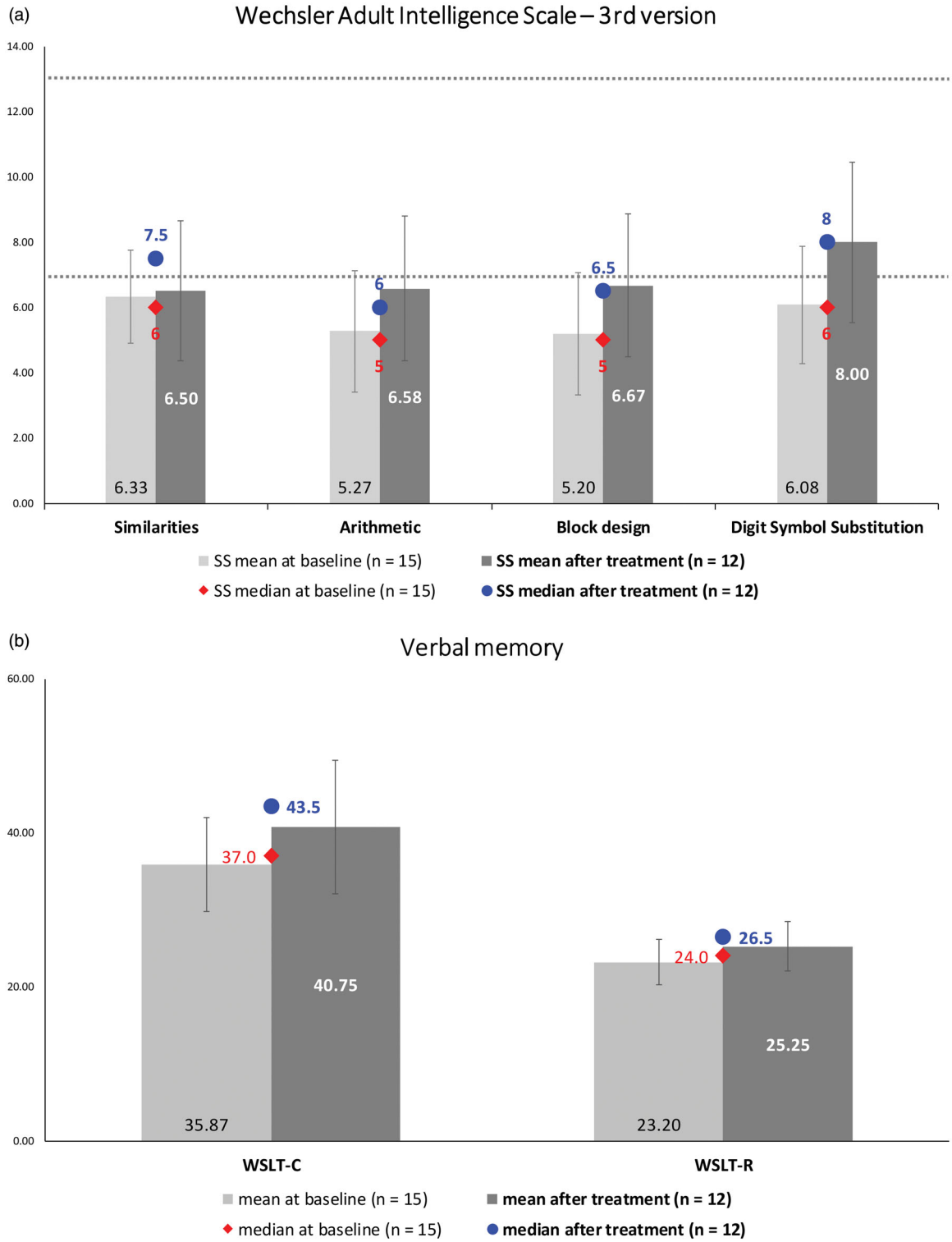

Figure 1. The change in neurocognitive performance assessment between the baseline (just before initiating the WBRT course) and immediately after the combined chemoradiation. (a) Executive functions reflected by Wechsler Adult Intelligence Scale (WAIS)—3rd version at baseline and post-treatment evaluations. Usually WAIS scores are presented in the form of scaled scores which are normally distributed and age-specific. Scaled scores of WAIS have a mean of 10 and a standard deviation of 3. Accordingly the dotted lines in this figure outline the range of one standard deviation (±1 SD) in WAIS-derived scores; scaled scores ranging from 7 to 13 are described as an average range. (b and c) Executive functions regarding verbal capability are disclosed by several specific NCF tests. Individually, SAVF: Semantic Association of Verbal Fluency; PASAT-R: Paced Auditory Serial Addition Test—Revised; WSLT-C: Word Sequence Learning Test—Correct; WSLT-R: Word Sequence Learning Test—Recognition. (d) Executive functions regarding mental shift are presented by the Trail-Making Test (part A and part B), recorded in the unit of seconds. The performance of patients to respond to TMT indicates the speed at which the assessed patient takes and finishes this NCF testing. Therefore, the less the time in seconds is taken to complete this assessment, the better performance this assessed patient owns. (e) Executive functions regarding mental shift are represented by the specific test of Modified Card Sorting Test (MCST), recorded in counts (scores). Namely, MCST-CC: Modified Card Sorting Test – Complete Categories; MCST-PE: Modified Card Sorting Test—Perseverative Errors. The performance of patients to carry out MCST-CC is absolutely and positively correlated with the scores of MCST-CC the patients get; by contrast, the scores the assessed patient gets on MCST-PE are negatively correlated with the executive function regarding mental shift that MCST-PE might indicate.

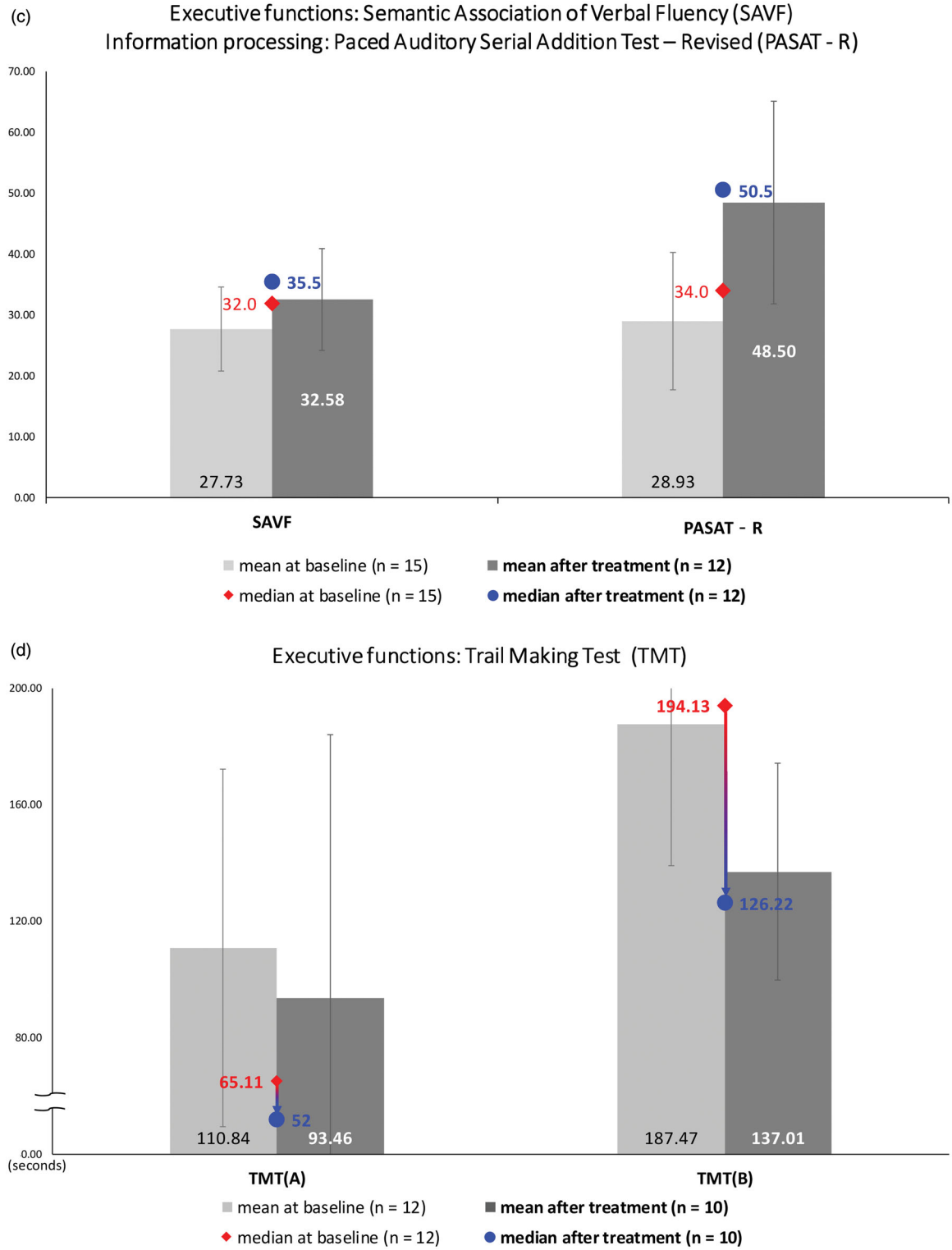

Figure 1. Continued.

Most of the other related research (Correa et al., 2009; Ferreri et al., 2017) used the pretreatment (pre-chemotherapy) NCF assessment as the baseline; therefore, our results should be interpreted and compared with those relevant reports cautiously. First, baseline NCF assessment was administered after the initial MTX courses and just before the subsequent WBRT course in our study. Therefore, the neurocognitive status at baseline in our study would represent the real situation, hypothetically evading the potential influence of the antecedent cytotoxic treatment with MTX before the WBRT course. Second, the changes in neurocognitive performance between baseline evaluation and

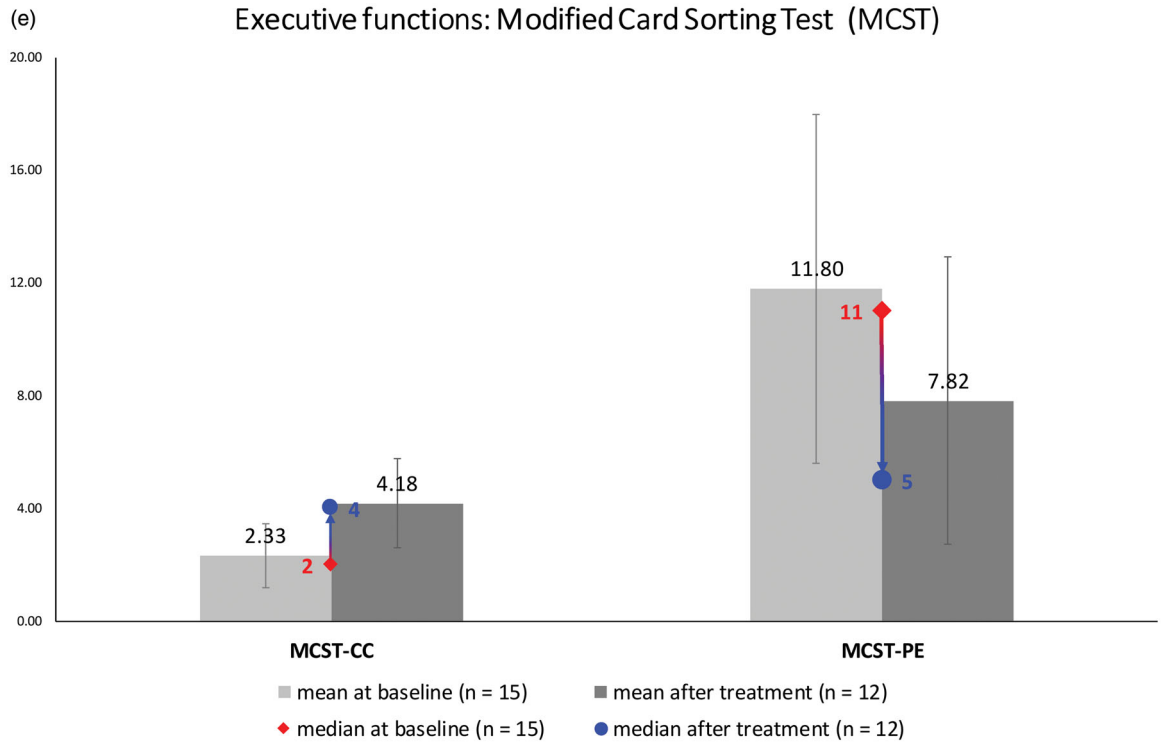

Figure 1. Continued.

Table 4. Comparing the neurocognitive scores between baseline and post-chemoradiation assessments.

	Baseline				Post chemoradiation				
NCF tests	Mean	SD	95% CI	Median	Mean	SD	95% CI	Median	Wilcoxon signed-rank *p* value
Similarities SS	6.3	2.6	4.9–7.7	6	6.5	3.4	4.4–8.6	7.5	0.836
Arithmetic SS	5.3	3.4	3.4–7.1	5	6.6	3.5	4.4–8.8	6	0.065
Block Design SS	5.2	3.4	3.3–7.1	5	6.7	3.4	4.5–8.9	6.5	0.027*
DSS SS	6.1	3.3	4.1–8.0	6	8.0	3.9	5.2–10.8	8	0.105
WSLT-C	35.9	11.1	29.7–42.0	37	40.8	2.5	32.0–49.5	43.5	0.062
WSLT-R	23.2	5.3	20.3–26.2	24	25.3	8.0	22.1–28.4	26.5	0.112
SAVF	27.7	12.5	20.8–34.7	32	32.6	13.2	24.2–41.0	35.5	0.306
PASAT-R	28.9	20.4	17.7–40.2	34	48.5	26.2	31.9–65.1	50	0.016*
TMT(A)	110.8	110.9	49.4–172.3	65.1	93.5	142.8	2.7–184.2	52	0.071
TMT(B)	187.5	76.2	139.0–235.9	194.1	137.0	52.1	99.8–174.3	126.2	0.059
MCST-CC	2.3	2.1	1.2–3.5	2	4.2	2.5	2.5–5.9	4	0.024*
MCST-PE	11.8	11.2	5.6–18.0	11	7.8	8.0	2.4–12.2	5	0.284
MMSE	22.3	5.6	19.2–25.4	21	25.2	5.0	22.0–28.4	26.5	0.083

SD: The Standard Deviation of the corresponding mean; SS: Scaled Scores; DSS SS: Digit Symbol Substitution Scaled Scores; WSLT-C: Word Sequence Learning Test—Correct; WSLT-R: Word Sequence Learning Test—Recall; SAVF: Semantic Association of Verbal Fluency; PASAT-R: Paced Auditory Serial Addition Test—Revised; TMT(A): Trail Making Test part A; TMT(B): Trail Making Test part B; MCST-CC: Modified Card Sorting Test—Complete Category; MCST-PE: Modified Card Sorting Test—Perseveration Error; MMSE: Mini-mental state examination.
*$p < .05$.

postchemoradiation assessments consistently exhibited a trend toward cognitive stabilization and even improvement without definite evidence of any harmful neurocognitive consequences. Therefore, our findings clearly implied that administering the WBRT course using a conventional dose/fractionation prescription did not jeopardize patients' cognitive performance at least shortly and 4 months after the WBRT course was completed.

Consistent with a large-scale phase II trial conducted by the International Extranodal Lymphoma Study Group (IELSG-32; Ferreri et al., 2017), despite the differences in the timeline when administering "baseline" NCF assessments in the current study and IELSG-32, neuropsychological testing after treatment completion showed a rapid improvement in most assessed cognitive functions in the present study. Nevertheless, whether the cognitive status at more extended posttreatment intervals might indicate a neurocognitive decline certainly merits further surveillance and investigation.

The techniques and prescription tailored to the delivery of WBRT in the current study should be mentioned and discussed. Owning to the great advances in RT-associated

techniques, a highly conformal CT treatment plan is widely used in the realm of radiation oncology. In addition, the principle of SIB has also been implemented in an attempt to escalate the focally tumoricidal dose. Thus, a highly conformal 3 D treatment planning plus the technique of multifocal SIBs has been well-established in RT delivery, such as head and neck cancers (Franceschini et al., 2013; Studer et al., 2006), anal cancers (Arcadipane et al., 2018; Tomasoa et al., 2016), and oligometastatic brain disease (Pokhrel et al., 2016), to achieve optimized dose distributions and contribute to more favorable tumor control and survival outcome.

Although patients' NCF status shortly and 4 months after the entire sandwiched course of combined chemoradiation demonstrated a robust tendency toward cognitive stabilization and even improvement free from a neurobehavioral decline in this study, this result should still be interpreted with caution as NCF decline resulting from WBRT could probably manifest or become evident after a longer follow-up (Doolittle et al., 2013; Ferreri et al., 2017). According to the final report of IELSG-32 randomized controlled trial (Ferreri et al., 2017), the effect of WBRT on cognitive functions might be underestimated because NCF scores during up to 2 years of follow-up were lacking. Regarding clinical implications and future directions, a more extended timeline for cognitive follow-up is required and will be implemented.

In addition, a potential learning effect due to periodic repetition (four-months between baseline and post-treatment evaluations) of NCF testing might potentially influence patients' neurocognitive performance. Although parallel tests were not used in our study to evade the risk of comparability drawbacks, the phenomenon of "learning effect" in nature, if existing, would represent the possibility that patients still preserved their neurobehavioral function of learning memory, indicating that at least patients' neurocognitive domain of learning memory did not decline considerably after the WBRT course. However, because no comparisons of NCFs were analyzed between patients with newly-diagnosed PCNSL and any controlled groups, the representativeness of patients' cognitive impairments and potential changes in this study is weakened.

Conclusions

Integrating functional outcomes including NCF assessments with commonly applied oncological outcomes would definitely help neuro-oncologists and radiation oncologists manage newly diagnosed PCNSL patients. Under the multidisciplinary treatment for patients with newly diagnosed PCNSL, multidomain NCFs can be stabilized after the course of conformal WBRT combined with MTX-based chemotherapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan, R.O.C. under Grant [CMRPG3E0951, CMRPG3D1403, CMRPG2G0472, CMRPG3J1011].

References

Arcadipane, F., Franco, P., Ceccarelli, M., Furfaro, G., Rondi, N., Trino, E., Martini, S., Iorio, G. C., Mistrangelo, M., Cassoni, P., Racca, P., Morino, M., & Ricardi, U. (2018). Image-guided IMRT with simultaneous integrated boost as per RTOG 0529 for the treatment of anal cancer. *Asia-Pacific Journal of Clinical Oncology*, *14*(3), 217–223. https://doi.org/10.1111/ajco.12768

Correa, D. D., Maron, L., Harder, H., Klein, M., Armstrong, C. L., Calabrese, P., Bromberg, J. E. C., Abrey, L. E., Batchelor, T. T., & Schiff, D. (2007). Cognitive functions in primary central nervous system lymphoma: Literature review and assessment guidelines. *Annals of Oncology*, *18*(7), 1145–1151. https://doi.org/10.1093/annonc/mdl464

Correa, D. D., Rocco-Donovan, M., DeAngelis, L. M., Dolgoff-Kaspar, R., Iwamoto, F., Yahalom, J., & Abrey, L. E. (2009). Prospective cognitive follow-up in primary CNS lymphoma patients treated with chemotherapy and reduced-dose radiotherapy. *Journal of Neuro-Oncology*, *91*(3), 315–321. https://doi.org/10.1007/s11060-008-9716-0

Correa, D. D., Shi, W., Abrey, L. E., DeAngelis, L. M., Omuro, A. M., Deutsch, M. B., & Thaler, H. T. (2012). Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro-Oncology*, *14*(1), 101–108. https://doi.org/10.1093/neuonc/nor186

DeAngelis, L. M., Seiferheld, W., Schold, S. C., Fisher, B., & Schultz, C. J. (2002). Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group study 93-10. *Journal of Clinical Oncology*, *20*(24), 4643–4648. https://doi.org/10.1200/jco.2002.11.013

DeAngelis, L. M., Yahalom, J., Thaler, H. T., & Kher, U. (1992). Combined modality therapy for primary CNS lymphoma. *Journal of Clinical Oncology*, *10*(4), 635–643. https://doi.org/10.1200/JCO.1992.10.4.635

Doolittle, N. D., Korfel, A., Lubow, M. A., Schorb, E., Schlegel, U., Rogowski, S., Fu, R., Dosa, E., Illerhaus, G., Kraemer, D. F., Muldoon, L. L., Calabrese, P., Hedrick, N., Tyson, R. M., Jahnke, K., Maron, L. M., Butler, R. W., & Neuwelt, E. A. (2013). Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma. *Neurology*, *81*(1), 84–92. https://doi.org/10.1212/WNL.0b013e318297eeba

Ferreri, A. J. M., Cwynarski, K., Pulczynski, E., Fox, C. P., Schorb, E., La Rosée, P., Binder, M., Fabbri, A., Torri, V., Minacapelli, E., Falautano, M., Ilariucci, F., Ambrosetti, A., Roth, A., Hemmaway, C., Johnson, P., Linton, K. M., Pukrop, T., Sønderskov Gørløv, J. … IELSG. (2017). Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: Results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *The Lancet Haematology*, *4*(11), E510–E523. https://doi.org/10.1016/s2352-3026(17)30174-6

Ferreri, A. J., Reni, M., Foppoli, M., Martelli, M., Pangalis, G. A., Frezzato, M., Cabras, M. G., Fabbri, A., Corazzelli, G., Ilariucci, F., Rossi, G., Soffietti, R., Stelitano, C., Vallisa, D., Zaja, F., Zoppegno, L., Aondio, G. M., Avvisati, G., Balzarotti, M., … Cavalli, F. (2009). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: A randomised phase 2 trial. *The Lancet*, *374*(9700), 1512–1520. https://doi.org/10.1016/s0140-6736(09)61416-1

Fine, H. A. (1993). Primary Central Nervous System Lymphoma. *Annals of Internal Medicine*, *119*(11), 1093. https://doi.org/10.7326/0003-4819-119-11-199312010-00007

Franceschini, D., Paiar, F., Meattini, I., Agresti, B., Pasquetti, E. M., Greto, D., Bonomo, P., Marrazzo, L., Casati, M., Livi, L., & Biti, G. (2013). Simultaneous integrated boost-intensity-modulated radiotherapy in head and neck cancer. *The Laryngoscope*, *123*(12), E97–E103. https://doi.org/10.1002/lary.24257

Hua, M.-S., Chang, S.-H., & Chen, S.-T. (1997). Factor structure and age effects with an aphasia test battery in normal Taiwanese adults. *Neuropsychology*, *11*(1), 156–162. 10.1037//0894-4105.11.1.156

Hua, M. S. (1986). Word Sequence Learning Test–Taiwanese Version. Chungli: Chung Yuan University, Department of Psychology.

Kasenda, B., Loeffler, J., Illerhaus, G., Ferreri, A. J. M., Rubenstein, J., & Batchelor, T. T. (2016). The role of whole brain radiation in primary CNS lymphoma. *Blood*, *128*(1), 32–36. https://doi.org/10.1182/blood-2016-01-650101

Levin, H. S. (1983). *Paced auditory serial addition task – Revised* [Unpublished manuscript]. University of Texas Medical Branch at Galveston, Neurosurgery Division.

Morris, P. G., Correa, D. D., Yahalom, J., Raizer, J. J., Schiff, D., Grant, B., Grimm, S., Lai, R. K., Reiner, A. S., Panageas, K., Karimi, S., Curry, R., Shah, G., Abrey, L. E., DeAngelis, L. M., & Omuro, A. (2013). Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: Final results and long-term outcome. *Journal of Clinical Oncology*, *31*(31), 3971–3979. https://doi.org/10.1200/jco.2013.50.4910

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, *12*(4), 313–324. https://doi.org/10.1016/S0010-9452(76)80035-4

Norden, A. D., Drappatz, J., Wen, P. Y., & Claus, E. B. (2011). Survival among patients with primary central nervous system lymphoma, 1973–2004. *Journal of Neuro-Oncology*, *101*(3), 487–493. 10.1007/s11060-010-0269-7

Pokhrel, D., Sood, S., McClinton, C., Shen, X., Lominska, C., Saleh, H., Badkul, R., Jiang, H., Mitchell, M., & Wang, F. (2016). Treatment planning strategy for whole-brain radiotherapy with hippocampal sparing and simultaneous integrated boost for multiple brain metastases using intensity-modulated arc therapy. *Medical Dosimetry*, *41*(4), 315–322. https://doi.org/10.1016/j.meddos.2016.08.001

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*(3), 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Reni, M., Ferreri, A. J. M., Garancini, P., & Villa, E. (1997). Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: Results of a critical review of the literature. *Annals of Oncology*, *8*(3), 227–234. https://doi.org/10.1023/a:1008201717089

Schaff, L. R., & Grommes, C. (2018). Updates on primary central nervous system lymphoma. *Current Oncology Reports*, *20*(2), 11. https://doi.org/10.1007/s11912-018-0666-1

Studer, G., Huguenin, P. U., Davis, J. B., Kunz, G., Lutolf, U. M., & Glanzmann, C. (2006). IMRT using simultaneously integrated boost (SIB) in head and neck cancer patients. *Radiation Oncology*, *1*(1), 7.

Tomasoa, N. B., Meulendijks, D., Nijkamp, J., Cats, A., & Dewit, L. (2016). Clinical outcome in patients treated with simultaneous integrated boost – Intensity modulated radiation therapy (SIB-IMRT) with and without concurrent chemotherapy for squamous cell carcinoma of the anal canal. *Acta Oncologica*, *55*(6), 760–766. https://doi.org/10.3109/0284186x.2015.1124141

Wechsler, D. (1997). Wechsler intelligence scale for adults. London: The Psychological Corporation.